Hot News

Should We Treat Chronic Hepatitis C in HIV with Peginterferon Alpha 2a or 2b?

Since 2001, the recommended therapy for patients with chronic hepatitis C virus (HCV) infection is a combination of pegylated interferon alpha (PEG-IFNα) plus ribavirin. The two commercially available preparations of PEG-IFNα (2a and 2b) differ in pegylation sites, molecular weight, and structure, resulting in significant differences in pharmacokinetic and pharmacodynamic properties. The registration trials of both PEG-IFNα for the treatment of chronic hepatitis C conducted almost 10 years ago yielded sustained virologic response (SVR) rates of 54% for PEG-IFNα 2b (Manns, et al. Lancet. 2001;358:958-65) and 56-63% for PEG-IFNα 2a respectively (Fried, et al. N Engl J Med. 2002;347:975-82; Hadziyannis, et al. Ann Intern Med. 2004;140:346-55). Accordingly, and in the absence of a head-to-head comparative trial, both PEG-IFNs were considered as equipotent.

The IDEAL study, a prospective, randomized trial sponsored by Schering-Plough, compared the efficacy of two different weekly doses of PEG-IFNα 2b (1.5 vs. 1.0 µg/kg) with a third control arm of PEG-IFNα 2a (180 µg), all in combination with weight-based ribavirin, in 3,000 US patients with HCV genotype 1 (McHutchison, et al. N Engl J Med. 2009;361:580-93). Although the rate of end-of-treatment response (ETR) was higher in patients treated with PEG-IFNα 2a than in those treated with PEG-IFNα 2b, there were no significant differences in SVR rates since relapses were more frequent using 2a than 2b (28 vs. 18%, respectively). However, ribavirin dosing, which is known to be closely related with relapse rates, and more importantly the dose-reduction schedules for anemia (according to labeled recommendations) were quite different and favored the PEG-IFNα 2b arms. Briefly, there was only one-step ribavirin reduction to 600 mg/day for PEG-IFNα 2a patients, while stepwise decreases of 200 mg/day were possible for PEG-IFNα 2b patients. Therefore, the design of the IDEAL study makes it difficult to establish a "correct" comparison between both PEG-IFNα molecules.

Another two prospective, randomized but "industry-independent" studies have just been released, in which head-to-head comparisons of PEG-IFNs are made. They are both single-center trials and have been conducted in Italy. In the first of them (Ascione, et al. Gastroenterology. 2010;138:116-22), the investigators treated 320 chronic hepatitis C-naive patients. This time the dose of ribavirin was the same for both groups of patients (1,000 mg/day for those with body weight < 75 kg and 1,200 mg/day for patients weighing ≥ 75 kg) and dose reductions for managing anemia were also identical, with stepwise decrements of 200 mg/day. The rates of early virologic response (EVR), ETR, and SVR were significantly higher in patients treated with PEG-IFNα 2a than 2b (Table 1), with no significant differences either in the incidence or severity of adverse events. Results were reproduced across all HCV genotypes. Moreover, PEG-IFNα 2a was again more effective than PEG-IFN 2b in the subset of patients with high baseline serum HCV RNA (> 500,000 IU/ml).

The second study (Rumi, et al. Gastroenterology. 2010;138:108-15) enrolled 431 patients with similar characteristics (naive to interferon, infected with distinct HCV genotypes, and with a similar proportion of liver cirrhosis). As in the previous study, PEG-IFNα 2a outperformed 2b in the intent-to-treat analysis across all HCV genotypes (Table 1).

Finally, a recent meta-analysis in which SVR to PEG-IFNα plus ribavirin was assessed in more than 4,000 HCV-monoinfected patients from eight different trials also showed a greater efficacy of PEG-IFNα 2a versus 2b (Awad, et al. Hepatology. 2009;50(Suppl):707-8). Altogether, these findings suggest that the antiviral efficacy of PEG-IFNα 2a is superior to 2b, and that the increased potency of the former could be particularly manifest in subjects with more elevated serum HCV RNA.

Scarce information exists comparing the efficacy of both PEG-IFNα molecules in HCV/HIV-coinfected patients. In a prospective, randomized, clinical trial including 182 patients naive for HCV therapy, 86 of whom were assigned to PEG-IFNα 2a and 96 to PEG-IFNα 2b, both together with ribavirin (800-1,200 mg/day) for 48 weeks,

Table 1. Response to peginterferon-ribavirin in head-to-head prospective trials in HCV-monoinfected patients

	Overall SVR		SVR HCV genotypes 1		SVR HCV genotypes 2/3	
	2a	2b	2a	2b	2a	2b
IDEAL*	41%	40%	41%	40%	–	–
Ascione, et al.	69%	54%	54%	40%	92/76%	78/71%
Rumi, et al.	66%	54%	48%	32%	96/65%	82/69%

*IDEAL trial included only HCV genotype 1 patients. SVR: sustained virologic response.

the overall SVR was 46% for 2a and 42% for 2b, without reaching significant differences (Laguno, et al. Hepatology. 2009;49:22-31), which could be attributed to the limited size of the study population. In contrast, in a retrospective analysis of 218 coinfected patients treated with either PEG-IFNα 2a or 2b, undetectable serum HCV RNA at weeks 4, 12, and 24 was more frequently attained using PEG-IFNα 2a than 2b (45 vs. 27% [p = 0.02]; 65 vs. 45% [p = 0.01]; and 75 vs. 55% [p = 0.01], respectively), regardless of HCV genotype (Vispo, et al. Antivir Ther. 2008;13:511-7), suggesting that also in the HIV setting, PEG-IFNα 2a outperformed 2b in the treatment of chronic hepatitis C.

In the era of new anti-HCV agents, triple therapy with PEG-IFNα plus ribavirin plus protease/polymerase inhibitors will soon become the standard hepatitis C therapy, at least for difficult-to-treat patients such as those infected with HCV genotype 1. In a recent randomized, phase II trial that compared the efficacy and safety of telaprevir dosed every 8 or 12 hours, along with either PEG-IFNα 2a or 2b in 161 HCV genotype 1 patients, higher rapid virologic response rates were obtained with the former than with the latter (> 80 vs. 67-69%, respectively); (Marcellin, et al. AASLD. 2009). These differences in early viral kinetics between the two PEG-IFNα forms may have implications for the duration of triple therapy, according to the response-guided strategy, and selection of drug resistance. All these issues must be investigated in future studies.

Javier García-Samaniego
Hepatology Unit, Hospital Carlos III
CIBEREHD
Madrid, Spain

HLA-C – A New Factor Influencing HIV Disease Progression

Specific alleles at HLA class I locus have shown a strong association with nonprogressive HIV disease in long-term nonprogressors (LTNP) and elite controllers. This is most likely due to an enhanced T-cell immune response, thanks to more adequate presentation of antigenic epitopes to cytotoxic T lymphocytes (CTL). In this regard, HLA-B antigens instead of HLA-A or HLA-C have been the main focus of research (Gao, et al. Nat Med. 2005;11:1290-2; Kiepiela, et al. Nature. 2004;432:769-75). HIV epitopes restricted by HLA-B*5701 or HLA-B*2703 generate a better response than those restricted by other alleles (Migueles, et al. Proc Natl Acad Sci USA. 2000;97:2709-14; Balla-Jhagjhoorsingh, et al. J Immunol. 1999;162:2308-14).

Three years ago, Fellay, et al. showed for the first time that a single nucleotide change (T→C) in a region 35 kb upstream of the HLA-C gene, which they called HLA-C 5', accounted for 6.5% of the viral set-point variation in HIV-1-infected individuals (Fellay, et al. Science. 2007;317:944-7). Last year, a genome-wide association study (or GWAS) conducted in LTNP identified another polymorphism within the same genomic region, which was significantly more frequent in this subset of patients (Limou, et al. J Infect Dis. 2009;199:419-26). Unfortunately, these authors could not assess the association of the single nucleotide polymorphism (SNP) previously reported by Fellay's team in their population since it was off the chip they used. It is remarkable that both SNP are only 1,700 bp distant from each other in the human genome.

Other studies have examined the relationship between HLA-C 5' alleles and HIV disease progression. Han, et al. analyzed 16 elite controllers and found that four of them carried a protective form of HLA-C 5' (Han, et al. AIDS. 2008;22:541-4). Moreover, in a homosexual cohort in Amsterdam, an association of the C-allele with lower plasma viremia and delayed HIV disease progression was found (van Manen, et al. AIDS. 2009;23:19-28). In line with these findings, we also found an increased prevalence of the HLA-C SNP in our cohort of long-term nonprogressors.

How can HLA-C SNP influence HIV disease progression? It seems that HLA-C 5' polymorphisms are in strong linkage disequilibrium with the HLA-B*5701 allele (Trachtenberg, et al. Genes Immun. 2009;10:673-7) that is closely associated with the LTNP status. This could suggest that the association of the HLA-C polymorphism with disease progression could be mediated through HLA-B*5701. However, Fellay, et al. have recently confirmed the independent role of HLA-C 5' variation on early control of HIV replication (Fellay, et al. PLoS Genet. 2009;5:e1000791). Moreover, a direct correlation between the C-allele and the level of expression of HLA-C proteins on the cell surface has been demonstrated (Thomas, et al. Nat Genet. 2009;41:1290-4). A higher number of HLA-C molecules on the cell surface might facilitate the presentation of HIV antigenic epitopes to CTL, resulting in a better immune control of HIV replication. In this regard, several polymorphisms at HIV polymerase gene have been reported to be specifically associated with HLA-C proteins (Matthews, et al. J Virol. 2008;82:8548-59).

While the HIV-nef protein selectively downregulates HLA-A and HLA-B proteins, it does not affect HLA-C expression (Cohen, et al. Immunity. 1999;10:661-1). Since orthologs of HLA-C have been identified in hominids but not in old world monkeys (Adams, et al. Immunol Rev. 2001;183:41-64), it can be assumed that the first SIV strains did not develop a defense mechanism against HLA-C, and that following the jump to humans, HLA-C is now playing an important role against HIV pathogenicity. HLA-C restricted CTL may be an important part of the HIV-specific immune response, and could account for as much as 54% of the total response, being functionally and phenotypically identical to HLA-A and HLA-B (Makadzange, et al. Eur J Immunol; in press). Altogether, these data support that the forgotten HLA-C must be considered as an important player in the control of HIV infection and that population variations in this locus could largely account for differences in HIV disease progression.

María Salgado
Laboratory of Molecular Biology
Infectious Diseases Department
Hospital Carlos III
Madrid, Spain

IL28B Genotyping - A Personalized Approach for Treating Chronic Hepatitis C

Chronic hepatitis C virus (HCV) infection is a first-degree public health problem worldwide, affecting around 175 million people. Current treatment with peginterferon plus ribavirin (PEG-IFN/RBV) provides cure to only half of patients and not all patients benefit to the same extent, as those infected with HCV genotypes 1 or 4, with high viremia, of older age, of black ethnicity, and with more advanced hepatic fibrosis tend to respond less. In addition, serious adverse events limit adherence to therapy. Patients experiencing rapid virologic response at week 4 of therapy have the highest chance of response following completion of therapy, while those without early virologic response at week 12 will unlikely respond to therapy. This is true in HCV-monoinfected as well as HIV/HCV-coinfected patients in whom response to therapy is generally lower (Soriano, et al. AIDS. 2007;21:1073-89).

The identification of baseline predictors of response to HCV therapy is desirable in order to optimize who should be treated and, conversely, who might defer current therapy. For the latter group of patients, waiting for the prompt arrival of new HCV antivirals may be the best option. Immunological predictors of treatment outcome, such as HCV-specific T-cell responses or factors involved in the interferon (IFN)-α signaling pathway, have been investigated with much interest. However, none has been found to be as strong as the recent discovery by three independent genome-wide association studies of single nucleotide polymorphisms (SNP) around the IL28B gene (Ge, et al. Nature. 2009;461:399-401; Suppiah, et al. Nat Genet. 2009;41:1100-4; Tanaka, et al. Nat Genet. 2009;41:1105-9). The SNP rs12979860, which consists of a nucleotide change of thymine (T) by cytosine (C), displayed the strongest association with HCV clearance on therapy. It is located on chromosome 19q13, 3 kb upstream of the *IL28B* gene and codes for IFN-λ3. The homozygous mutant genotype CC is associated with more than twofold greater rate of sustained virologic response than the heterozygous genotype CT or the wild-type homozygous genotype TT in different population groups (Ge, et al. Nature. 2009;461:399-401), and apparently across different HCV genotypes (McCarthy, et al. Gastroenterology. [in press]). A role for *IL28B* polymorphisms in spontaneous HCV clearance has subsequently been established (Thomas, et al. Nature. 2009;461:798-801; Rauch, et al. Gastroenterology. [in press]).

The impact of the *IL28B* gene SNP in HIV/HCV-coinfected individuals has only recently been unraveled. It was at CROI 2010 (San Francisco, February 2010) that several groups from North America and Western Europe provided information on this population for the first time (Nattermann, et al. paper 164; Rallon, et al. paper 165LB; Pineda, et al. paper 656). All three studies concluded that the rs12979860 SNP located near the *IL28B* gene exerts a strong impact on the sustained virologic response likelihood in coinfected patients. Moreover, as in HCV-monoinfected individuals, CC genotype carriers were more prone to clear HCV spontaneously following initial exposure. Interestingly, all these effects seemed to apply to HCV genotypes 1 and 4, but be absent in HCV genotype 3 (Rallon, et al. paper 165LB; Pineda, et al. paper 656).

Beyond the relevance for the investigation of new therapeutic strategies against HCV that include IFN-λ3, the recognition that *IL28B* polymorphisms may influence natural HCV clearance as well as virus elimination following IFN-based therapy supports that *IL28B* genotyping should be incorporated as part of the HCV treatment decision algorithm in HIV/HCV-coinfected patients. Further studies are needed to unravel the biological mechanisms by which polymorphisms near the *IL28B* gene can influence the response to HCV therapy to such a strong extent.

Norma I. Rallón
Molecular Biology Laboratory
Infectious Diseases Department
Hospital Carlos III
Madrid, Spain

WHO Releases New HIV Guidelines Aimed At Resource-Limited Settings

World AIDS Day on December 1 has traditionally been a great opportunity for different agencies to issue updated HIV/AIDS guidelines. In late 2009, the U.S. Department of Health and Human Services (DHHS) (http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf) and the European AIDS Clinical Society (EACS) (http://www.europeanaidsclinicalsociety.org/Guidelines2009/index.htm) issued the latest updates of their guidelines. These recommendations are widely used by clinicians in Western countries. Following the same steps, on the eve of World AIDS Day 2009, the World Health Organization (WHO) released new recommendations for using antiretroviral therapy in adults and adolescents (http://www.who.int/entity/hiv/pub/arv/rapid_advice_art.pdf), prevention of mother-to-child transmission (MTCT) (http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf) and infant feeding (http://whqlibdoc.who.int/publications/2009/9789241598873_eng.pdf). The full guidelines publication is expected to appear in early 2010. This document updates prior WHO guidelines released in 2006. The revised WHO recommendations will have a significant impact in resource-limited countries, where they will serve as a reference for best clinical practice, allowing to set national standards for HIV treatment and care.

The WHO key messages focus on two areas: (i) when to start antiretroviral therapy (ART), and (ii) what antiretrovirals to use in adults, adolescents, pregnant women, as well as tuberculosis (TB) and hepatitis B (HBV) coinfected individuals.

The optimal time to start antiretroviral therapy in asymptomatic persons has been one of the central controversies in the care of HIV patients. Most high-income countries have revised their national ART guidelines to endorse an earlier start, much earlier in the course of the disease than previously recommended. For instance, the DHHS now offers a moderate-to-strong recommendation for treatment of asymptomatic individuals with CD4 counts between 350-500 cells/mm^3. The 2006 WHO guidelines recommended

that ART be started in patients with advanced clinical disease and/or CD4 counts below 200 cells/mm^3. The new 2009 recommendations promote earlier treatment, generally when CD4 counts fall to less than 350 cells/mm^3, regardless of clinical symptoms. These new recommendations are based on a solid body of evidence that indicates that rates of death, morbidity, as well as of HIV and tuberculosis transmission are all reduced when ART is started earlier.

On the question of when to initiate ART in TB patients, the WHO panel recommends starting ART in all HIV-infected individuals with active tuberculosis irrespective of CD4 cell counts. The optimal timing for the initiation of ART in these patients remains unclear, although there is clear support for treating the two diseases concomitantly, starting TB treatment first and ART as soon as possible. Data from the SAPIT trial (Abdool-Karim, et al. N Engl J Med. 2010;362:697-706) supports this recommendation, at least for patients with CD4 counts below 500 cells/mm^3.

While the 2006 WHO guidelines recognized the critical role of stavudine-containing regimens as part of first-line antiretroviral therapy, given its low cost, low rate of resistance and relatively good short-term safety profile, the recognition of the high risk of lipodystrophy and mitochondrial toxicity has discouraged its use in the new guidelines. The WHO is now recommending that all governments adopt national policy guidelines that promote a transition to less toxic first-line drugs, avoiding the use of stavudine without jeopardizing sustainability and access to treatment.

New guidelines have also issued revised recommendations on when to start treatment in HIV/HBV-coinfected individuals. The advice is to start ART in this population when there are criteria for treating hepatitis B, irrespective of CD4 cell counts or WHO clinical stage. Of note, the use of at least two agents with activity against HBV (tenofovir and lamivudine or emtricitabine) is strongly advised in order to minimize the risk for developing HBV drug resistance. Lamivudine has been and remains pivotal to all first-line HAART regimens in resource-limited settings. However, the efficacy of lamivudine against HBV is limited by the occurrence of drug resistance, which develops in 50% of patients after two years of monotherapy and in 90% after four years (Matthews, et al. AIDS. 2006;20:863-70). Selection of lamivudine-resistant HBV must be avoided, given that it precludes the clinical benefit of therapy, impairs response to most other anti-HBV agents (cross-resistance), favors selection of HBV vaccine escape mutants, and may promote transmission of drug-resistant HBV (Soriano, et al. Clin Infect Dis. 2008;47:1486-9). Additional anti-HBV drugs less vulnerable for the selection of HBV resistance (particularly tenofovir) should be made available for the treatment of all HIV/HBV-coinfected individuals in these settings.

The WHO prevention of mother-to-child transmission recommendations refer to two key approaches: (i) lifelong ART for HIV-positive women in need of treatment and (ii) prophylaxis, or short-term provision of antiretrovirals to prevent HIV transmission from mother to child in women who do not need ART for their own health. In all these women, the 2009 recommendations promote longer use of ART in pregnancy, starting at 14 weeks instead of the 28 weeks of prior guidelines, and continuing through the end of the breastfeeding period. The WHO now recommends that breastfeeding continue until the infant reaches 12 months of age, provided that the HIV-positive mother and/or baby are taking antiretrovirals during this period. This change in the WHO guidelines is particularly welcome as peripartum single-dose nevirapine is no longer recommended to prevent mother-to-child transmission. This strategy is now discouraged because it can select for drug-resistant HIV and compromise subsequent response to nevirapine-based regimens in women and their infants (Lockman, et al. N Engl J Med. 2007;356:135-47). However, the WHO guidelines still allow the use of monotherapy for mothers and infants in several circumstances, which is viewed as a mistake by many.

Finally, the 2009 WHO recommendations outline an expanded role for laboratory monitoring to improve the quality of HIV treatment and care. A greater access to CD4 count and viral load monitoring is encouraged, although access to ART must not be denied when these tools are not available. The WHO guidelines note that the main challenge lies in increasing the availability of ART in many resource-limited countries. Although much has been accomplished, the expansion of ART and prevention of mother-to-child transmission services continues to be hindered by weak infrastructures, limited human and financial resources, and poor integration of HIV-specific interventions within broader health services. With nearly 34 million people living with HIV, and an annual incidence of new infections of approximately 2.7 million, the HIV epidemic continues to be a major challenge for global health. Hopefully, the implementation of the new WHO recommendations on a wide scale will improve the health of people affected by HIV and reduce the number of new HIV infections.

Pablo Rivas
Tropical Medicine Unit, Infectious Diseases Department
Hospital Carlos III
Madrid, Spain

Pilar Ustero
BIPAI, Baylor College of Medicine
Mbabane, Swaziland